PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 487/10, A61K 31/47

A1

(11) International Publication Number: **WO 99/00393**

(43) International Publication Date: 7 January 1999 (07.01.99)

(21) International Application Number: PCT/KR98/00185

(22) International Filing Date: 26 June 1998 (26.06.98)

(30) Priority Data:

1997/27806	26 June 1997 (26.06.97)	KR
1998/1609	20 January 1998 (20.01.98)	KR

(71) Applicant *(for all designated States except US)*: DONG WHA PHARMACEUTICAL INDUSTRIAL CO., LTD. [KR/KR]; 5, Soonwha-dong, Choong-ku, Seoul 100-130 (KR).

(72) Inventors; and

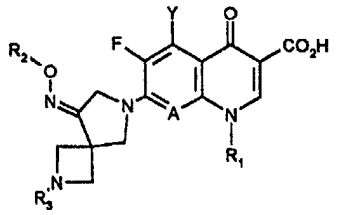
(75) Inventors/Applicants *(for US only)*: YOON, Sung-Joon [KR/KR]; 1420-11, Sinlim 5-dong, Kwanak-ku, Seoul 151-015 (KR). CHUNG, Yong-Ho [KR/KR]; #301-204, Saemmaeul Apt., Hogye-dong, Dongan-ku, Anyang, Kyunggi-do 431-080 (KR). LEE, Chi-Woo [KR/KR]; #207-201, Jugong Apt., Sanbon-dong, Kunpo, Kyunggi-do 435-040 (KR). OH, Yoon-Seok [KR/KR]; #207, Hyunam Apt., 164-11, Anyang 7-dong, Manan-ku, Anyang, Kyunggi-do 430-017 (KR). KIM, Nam-Doo [KR/KR]; #102-306, Hyundai 1-cha Apt., 628, Okryun-dong, Yonsu-ku, Inchon 406-050 (KR). LIM, Jae-Kyung [KR/KR]; #3-202, Yuchang Villa, 198-66, Anyang 7-dong, Manan-ku, Anyang, Kyunggi-do 430-017 (KR). JIN, Yoon-Ho [KR/KR]; 96-39, Sinlim 2-dong, Kwanak-ku, Seoul 151-012 (KR).

(74) Agent: PARK, Sa-Ryong; #301 Chongho Building, 823-5, Yoksam-dong, Kangnam-ku, Seoul 135-080 (KR).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: QUINOLONE CARBOXYLIC ACID DERIVATIVES



(1)

(57) Abstract

The present invention relates to quinolonecarboxylic acid derivatives having more excellent and broad antibacterial activities than the existing quinolone-series antibiotics. More specifically, it pertains to novel quinolonecarboxylic acid derivatives represented by formula (1), which have a derivative of 7-[8-(alcoxyimino)-2,6-diazaspiro[3,4]oct-6-yl] as a substituent, and pharmaceutically acceptable salts and isomers thereof; wherein A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; and R_3 is H or C_{1-4} alkyl.

FOR THE PURPOSES OF INFORMATION ONLY

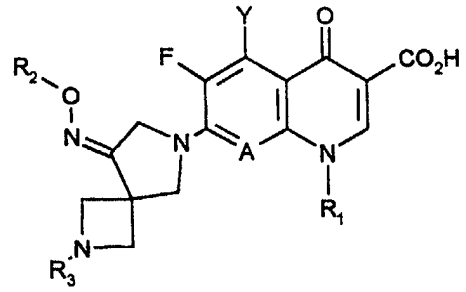
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

QUINOLONE CARBOXYLIC ACID DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to quinolonecarboxylic acid derivatives having more excellent and broad antibacterial activities than the existing quinolone-series antibiotics. More specifically, it pertains to novel quinolonecarboxylic acid derivatives represented by following formula 1, which have a derivative of 7-[8-(alkoxyimino)-2,6-diazaspiro[3.4]oct-6-yl] as a substituent, and pharmaceutically acceptable salts and isomers thereof:



1

Wherein, A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; and R_3 is H or C_{1-4} alkyl.

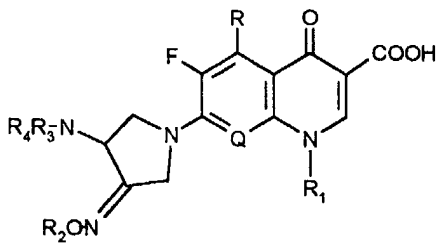
BACKGROUND OF THE INVENTION

Quinolonecarboxylic acid derivatives are synthetic antibiotics which are well known to be useful for the treatment of infective diseases in human and animals due to their potent and broad antibacterial activities. Quinolone-series antibiotics such as norfloxacin, ofloxacin and ciprofloxacin are currently used very usefully for the treatment of human diseases and their efficacies are acknowledged. However, these medicines have a problem that: even though they show excellent antibacterial activities against gram-negative bacteria, they still show ordinary or relatively low

antibacterial activities against gram-positive bacteria. Accordingly, there have been various studies for solving such problems of existing quinolone-series antibiotics and, finally, sparfloxacin having improved antibacterial activities against gram-positive bacteria has been developed.

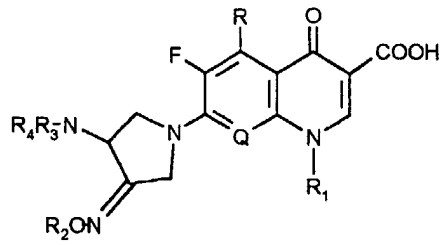
However, this compound still shows weak antibacterial activities against *Streptococci*, methicillin resistant *Staphylococcus aureus*(MRSA) and other currently increasing quinolone-resistant strains. These strains are well known as pathogens of the respiratory infections. Therefore, there are increasing needs for the development of improved quinolone antibiotics which exhibit excellent antibacterial activities against such quinolone-resistant strains.

On the other hand, Korean patent laid-open publication Nos. 96-873, 96-22501 and 96-22502, and EP688772A1 disclose quinolone-series antibacterial agents of following formulae 16, 17 and 18:



16

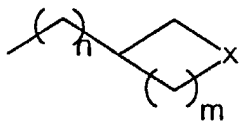
Wherein, Q is C-H, C-F, C-Cl, C-OH, C-O-CH_3 or N; R is H, methyl or amino; R_1 is cyclopropyl, ethyl, or phenyl substituted with more than one fluorine atom; R_2 is H, C_{1-4} straight or branched alkyl, phenyl or allyl.



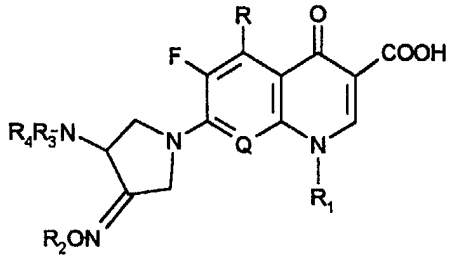
17

Wherein, R is H, methyl or amino; Q is C-H, C-F, C-Cl, C-CH_3,

C-O-CH_3 or N; R_1 is cyclopropyl, ethyl, or phenyl substituted with one or more fluorine atoms; R_2 is C_3-C_4 branched alkyl such as t-butyl and cyclopropylmethyl, C_3-C_6 alkyl having a triple bond such as propagyl and homopropagyl, 2-haloethyl, methoxymethyl, methoxycarbonylmethyl, or a group having the following formula:



Wherein, n is 0 or 1; m is 0, 1 or 2; x is methylene, O or N; R_3 and R_4 are independently H or C_1-C_3 alkyl group, or they may form a ring with a nitrogen group to which they are attached.



18

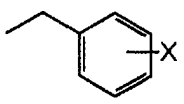
Wherein,

R is H, methyl or amino group;

Q is C-H, C-F, C-Cl, C-CH_3, C-O-CH_3 or N;

R_1 is cyclopropyl, ethyl, or phenyl group substituted with one or more fluorine atom;

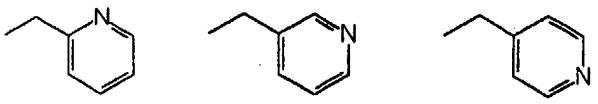
R_2 is a group of following formula a :



a

Wherein, X is 2-, 3- or 4-fluoro, cyano, nitro, methoxy, methyl or C_1-C_4 alkyl group, or 2,4-difluoro group;

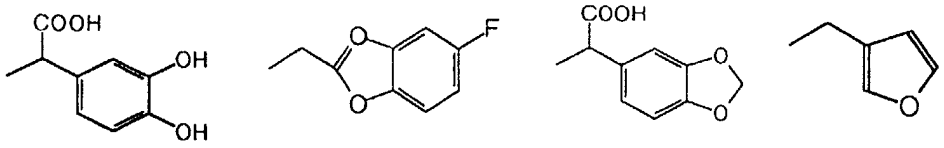
a group of following formula b:



b

; or

an arylmethyl group containing a hetero group of following formula c:

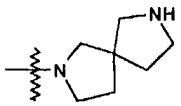


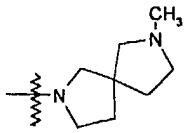
c

R_3 and R_4 are independently H or C_1-C_3 alkyl group, or they may form a ring with a nitrogen group to which they are attached.

The above compounds are different from the compound of the present invention of the formula 1 in their structures. Specifically, in the compounds disclosed in Korean Patent laid-open publication Nos. 96-873, 96-22501 and 96-22502, and EP688772 A1, an alkoxyimino group is substituted on the pyrrolidine ring, which is a substituent at the 7-position, and the substituents adjacent to the alkoxyimino group such as amino, alkylamino, aminomethyl, alkylaminomethyl are attached to the pyrrolidine ring as a straight chain form. In contrast, in the compounds of the present invention, the pyrrolidine ring substituted at the 7-position having an oxime and its derivatives, forms a diazaspiro compound with an azetidine structure. Accordingly, the compounds of the present invention are different from those of the above patent laid-open publications in their structures. In terms of antibacterial activities, the compounds of the present invention show strong antibacterial activities against the recently-increasing quinolone-resistant strains, while the compounds of the above patent laid-open publications exhibit very weak antibacterial activities against the quinolone-resistant strains.

Further, although EP265230 A1 discloses the substitution of diazaspiro compound at 7-position of the quinolone derivative, it specifically discloses only 2,7-diazaspiro[4.4]nonane and 2-methyl-2,7-diazaspiro[4.4]nonane compounds of the following formulae





and does not specifically disclose 2,6-diazaspiro[3.4]octane compound as disclosed in the present invention. Moreover, there is no mention about the alkoxyimino group introduced in the 2,6-diazaspiro[3.4]octane substituent on the 7-position as disclosed in the present invention. Accordingly, the compounds of the present invention are different from those of the above-mentioned patent laid-open publications in terms of structure. As to antibacterial activities, the compounds of the present invention exhibit excellent antibacterial activities against the existing quinolone-resistant strains as well as against both of gram-negative and gram-positive bacteria, while the compounds of the above-mentioned patent laid-open publications have ordinary antibacterial activities against gram-negative and gram-positive bacteria,

The present inventors have endeavored constantly to develop novel quinolonecarboxylic acids which exhibit excellent antibacterial activities against both of gram-negative and gram-positive bacteria, as well as improved antibacterial activities against such problematic strains as *Streptococci*, methicillin resistant *Staphylococcus aureus*(MRSA) and other currently increasing quinolone-resistant strains.

Finally, the present inventors have accomplished the present invention by discovering that quinolonecarboxylic acids substituted with 7-[8-(alkoxyimino)-2,6-diazaspiro[3.4]oct-6-yl] at the 7-position show excellent antibacterial activities against the above-mentioned strains.

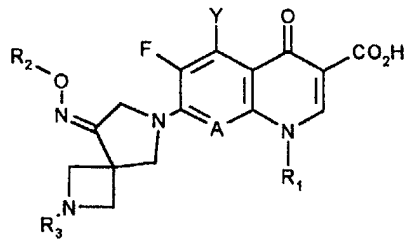
SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide novel quinolonecarboxylic acid derivatives of the above formula 1, and pharmaceutically acceptable salts and isomers thereof, which exhibit excellent antibacterial activities against both of gram-negative and gram-positive bacteria and, especially, show superior antibacterial activities against the methicillin-resistant strains, as well as against the existing quinolone-resistant strains.

Another object of the present invention is to provide processes for preparing the novel quinolonecarboxylic acid derivatives of the formula 1.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is characterized by quinolonecarboxylic acid derivatives represented by following formula 1, and pharmaceutically acceptable salts and isomers thereof:



1

Wherein, A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; and R_3 is H or C_{1-4} alkyl.

The present invention is described in more detail as follows.

According to the present invention, the typical examples of quinolone carboxylic acid derivatives of the above formula 1 may be listed as follows:

1-cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-6,8-difluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-6-fluoro-8-chloro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-(2,4-difluorophenyl)-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[8-(ethoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

1-cyclopropyl-5-amino-6,8-difluoro-7-[8-(ethoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid,

1-cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-6,8-difluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid,

1-cyclopropyl-6-fluoro-8-chloro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, and

1-cyclopropyl-5-amino-6,8-difluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3.4]oct-6-yl]-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid.

The quinolonecarboxylic acid derivatives of the present invention represented by formula 1 have a double bond in the pyrrolidine ring at the 7-position and, accordingly, geometric isomers of cis- or trans-form may be present. The present invention includes all of such geometric isomers.

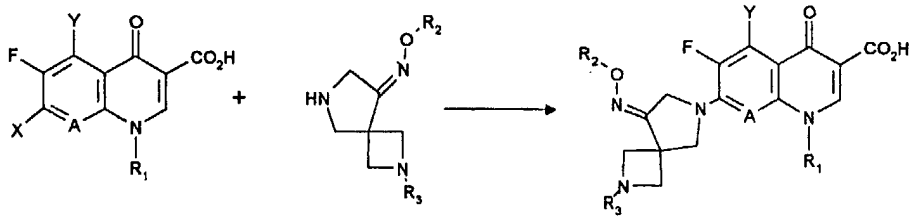
A pharmaceutically acceptable salts may be prepared from the quinolonecarboxylic acid derivatives of the present invention represented by formula 1, in accordance with some ordinary methods in the art to which the present invention pertains. As one kind of such salts, an acid addition salt may be prepared, and exemplary acids to be used therefor include an inorganic acid such as hydrochloric acid, phosphoric acid and sulfuric acid; and an organic acid such as methane sulfonic acid, p-toluene sulfonic acid, acetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, manderic acid and glucuronic acid. In addition, a cation such as sodium or potassium ion may also be used for the preparation of pharmaceutically acceptable salts.

Further, the present invention includes the process of preparing the quinolonecarboxylic acid derivatives represented by formula 1.

The quinolonecarboxylic acid derivatives of the present invention of the formula 1 may be prepared by any one of two methods represented by following Reaction schemes 1 and 2.

In the following reaction scheme 1, the compound of following formula 2 is subjected to coupling reaction with the compound of following formula 3 to obtain the desired compound of the present invention, i.e., a quinolonecarboxylic acid derivative represented by following formula 1.

[Reaction scheme 1]



2 3 1

Wherein, A, Y, R_1, R_2 and R_3 are respectively as definded above, and X is a halogen atom, preferably, fluorine or chlorine. The compound of formula 2 may be prepared in accordance with the method described in

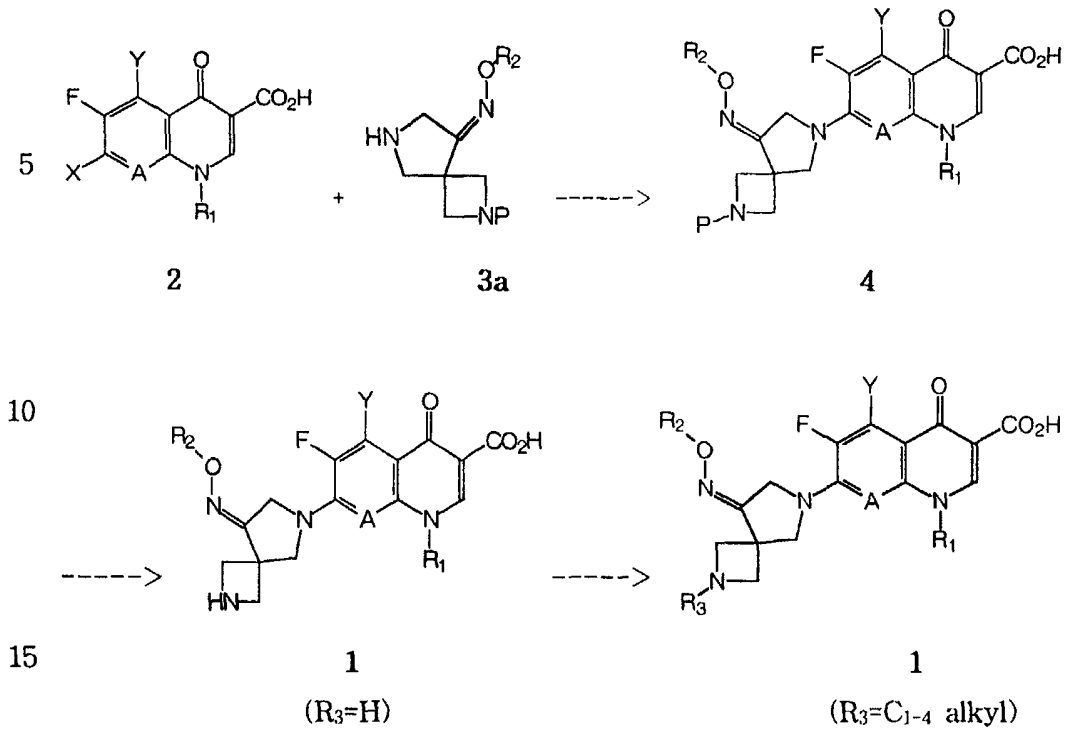
U. S. Patent No. 4,382,892. The compound of formula 3 may be used in the form of a free base or an acid salt, and the acid salt may be formed by using an acid such as hydrochloric acid, acetic acid and trifluoroacetic acid.

To explain the above reaction scheme in more detail, the coupling reaction of the compound of formula 2 with the compound of formula 3 are carried out under the presence of a solvent with the addition of a suitable base(acid acceptor) to obtain a quinolonecarboxylic acid derivative represented by formula 1. The reaction may be completed preferably at 0 to 200℃ for 1 to 24 hours with stirring.

As the solvent used in the above reaction, acetonitrile, dimethyl formamid(DMF), dimethylsulfoxide(DMSO) and pyridine are preferred. As the base(acid acceptor), it is preferred to use inorganic bases such as sodium hydrogencarbonate, calcium carbonate, and sodium carbonate, or organic bases such as triethylamine, diisopropylethylamine, pyridine, lutidine, N,N-dimethylaniline, N,N-dimethylaminopyridine, 1,8-diazabicyclo[5,4,0]undec-7-ene(DBU), 1,5-diazabicyclo[4,3,0]nonene-5(DBN), and 1,4-diazabicyclo[2,2,2]octane(DABCO). Further, the reaction efficiency may be increased by using an excessive amount(2 to 10 mole equivalents) of the compound of formula 3 as an acid acceptor. The reaction rate may increase by using an ion-exchange resin. Exemplary ion-exchange resin may include Amberlite® IRA-420, Amberlite® IRA-900 and Amberlite® IRA-64.

In the second preparation process(Reaction scheme 2), the compound of following formula 2 is subjected to coupling reaction with the compound of following formula 3a to prepare the desired compound of the present invention, i.e., a compound represented by following formula 1 wherein R_3 is H, via an intermediate of following formula 4. Further, the compounds of formula 1 wherein R_3 is C_{1-4} alkyl may be prepared by reductive alkylation of the compounds of formula 1 wherein R_3 is H with lower aldehydes.

[Reaction scheme 2]



Wherein, A, X, Y, R_1, R_2 and R_3 are respectively as definded above, and P is an amine protecting group.

The compound of formula 3a may be used in the form of a free base or an acid salt, and the acid salt may be formed by using an acid such as hydrochloric acid, acetic acid and trifluoroacetic acid. Further, exemplary amine protecting groups(P) of the compound of formula 3a include formyl, acetyl, trifluoroacetyl, benzoyl, alkoxycarbonyl(e.g., ethoxycarbonyl, *t*-butoxycarbonyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl), benzyl, *p*-methoxybenzyl and trityl.

The above reaction is carried out under the same condition as illustrated in Reaction scheme 1 for the coupling reaction of the compound of formula 2 with the compound of formula 3. The amine protecting

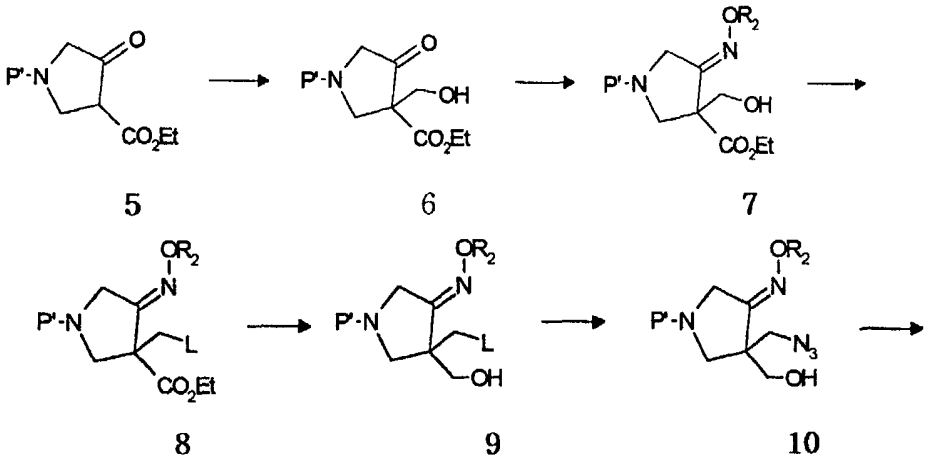
group(P) of the compound of formula 4 thus obtained from the condensation reaction is removed by an alkali hydrolysis or a general deprotection reaction to obtain the compound of formula 1.

For example, the compound of formula 4 is reacted in a solvent under the presence of an acid or base at a temperature ranging from room temperature to 120℃ to remove the amine protecting group(P). As an acid for use in the deprotection reaction, an inorganic acid such as hydrochloric acid, bromic acid and sulfuric acid, or an organic acid such as acetic acid, trifluoroacetic acid, formic acid, *p*-toluenesulphonic acid may be used. Further, in case that the amine protecting group(P) is a benzyl, p-methoxybenzyl, benzyloxycarbonyl, p-methoxybenzyloxycarbonyl or trichloroethoxycarbonyl group, the amine protecting group(P) may be removed by the reduction under the hydrogen atmosphere at a temperature ranging from 5 to 100℃ using palladium, Raney nickel or platinum.

On the other hand, the compounds of formula 1 wherein R_3 is C_{1-4} alkyl may be prepared by reductive alkylation of the compounds of formula 1 wherein R_3 is H with C_{1-4} aldehyde under a weak acidic condition by using sodiumcyanoborohydride as a reducing agent at 0 to 50℃.

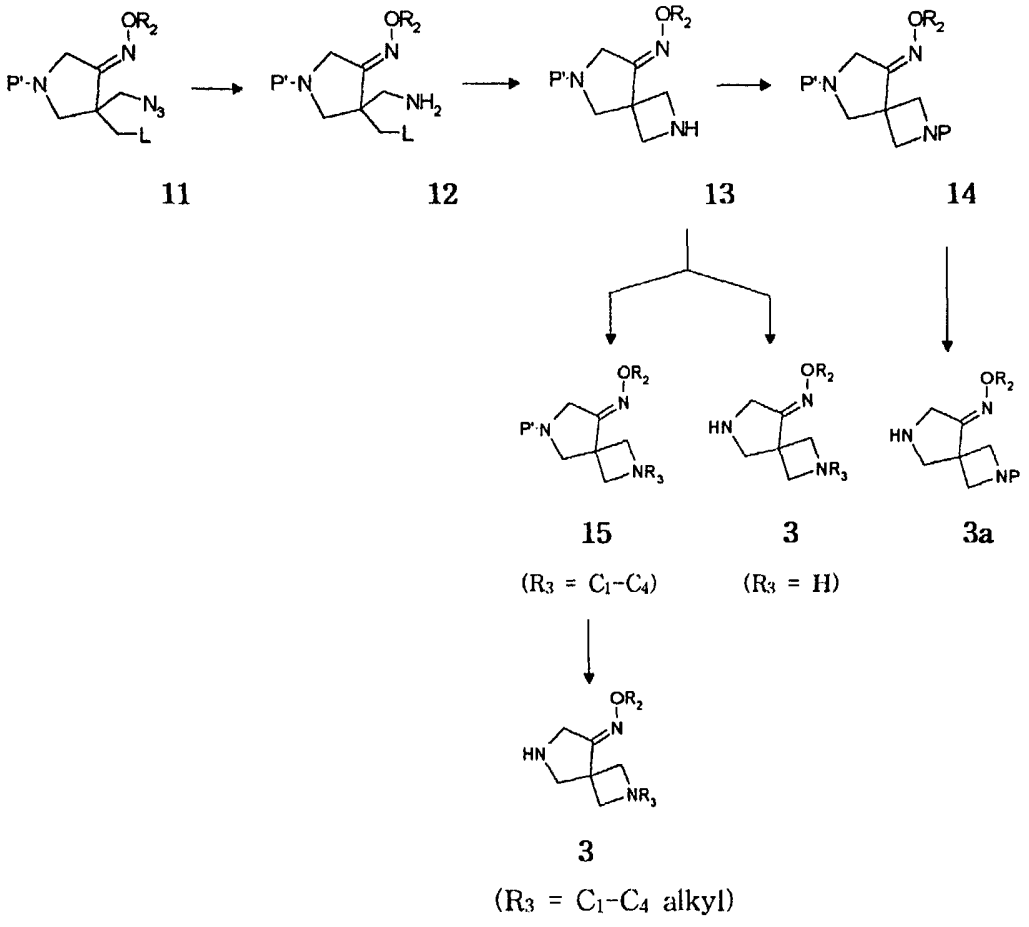
The compounds of formulae 3 and 3a, which are also the starting materials of the present invention, may be prepared by the following Reaction scheme 3.

[Reaction scheme 3]



5 6 7

8 9 10



Wherein, R_2 and R_3 are as defined above; L is methanesulfonyloxy, *p*-toluenesulfonyloxy, or halogen, preferably fluorine or chlorine; and P′ is an amine protecting group such as formyl, acetyl, trifluoroacetyl, benzoyl, alkoxycarbonyl(e.g., ethoxycarbonyl, *t*-butoxycarbonyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, trichloroethoxycarbonyl), benzyl, *p*-methoxybenzyl and trityl.

To explain the process of Reaction scheme 3 in detail, a ketoester compound(formula 5) is reacted with an aqueous formalin solution at 0 to room temperature under the presence of a base to obtain a hydroxyketone compound(formula 6). Suitable bases for this reaction include sodium carbonate, calcium carbonate, sodium hydrogen carbonate, sodium

hydroxide and calcium hydroxide, and suitable solvents include alcohols such as methanol, ethanol and isopropyl alcohol. The compound of formula 6 is reacted with an alkoxylamine to obtain an alkoxyimino pyrrolidine derivative compound of formula 7 in high yields. In this reaction, pyridine may be used as a solvent, as well as a base. Further, in case that water, tetrahydrofuran or an alcohol(methanol, ethanol, etc.) is used as a solvent, an inorganic base such as sodium hydrogen carbonate and sodium acetate may also be used together with such solvent. In order to convert an hydroxy group(-OH) in the compound of formula 7 to a suitable leaving group L[methanesulfonyloxy(-OMs), *p*-toluenesulfonyloxy(-OTs), halogen], the hydroxy group is reacted with methanesulfonyl chloride or *p*-toluenesulfonyl chloride under the presence of an organic base such as triethylamine and pyridine at a temperature ranging from 0 to 50℃ to obtain the compound of formula 8 wherein the hydroxy group is substituted with leaving group L. On the other hand, the compound of formula 8 may also be obtained by converting the hydroxy group(-OH) in the compound of formula 7 to halogen according to a conventional method. In the representative example of such halogenation reaction, pyridine is added to triphenylphosphine and carbontetrabromide(J. Chem. Soc, Perkin Trans. 1, 3549, 1997) and then reacted with the compound of formula 7 to obtain the bromide compound of formula 8. The ester group of the compound of formula 8 thus obtained is reduced by using a suitable reducing agent at a temperature ranging from 0 to reflux temperature of used solvent to obtain the alcohol compound of formula 9 in a good yield. Representative reducing agent for this reaction is sodium borohydride and the reactivity of sodium borohydride increases by using it together with a lithium salt(lithium chloride or lithium bromide). When sodium azide is reacted with leaving group L in the compound of formula 9, an azidomethyl pyrrolidine compound(formula 10) is obtained. As a solvent for this reaction, dimethyl formamide(DMF) or dimethyl sulfoxide(DMSO) is preferred. In order to convert a hydroxy group in the azidomethyl pyrrolidine compound(formula

10) to suitable leaving group L[methanesulfonyloxy(-OMs), *p*-toluenesulfonyloxy(-OTs) or halogen], the same reaction as in the conversion of the compound of formula 7 to the compound of formula 8 is conducted under the same condition to obtain the compound of formula 11 wherein the hydroxy group is converted to leaving group L, in a good yield. The azido group in the compound of formula 11 is reduced by using a metal catalyst such as platinum, palladium on carbon(Pd/C) and Raney nickel, or reduced by using triphenylphosphine or triphenylphosphite in an inert solvent such as tetrahydrofuran to obtain aminomethyl pyrrolidine compound(formula 12) in a good yield. When the compound of formula 12 is heated at 50 to 130℃ under the presence of a suitable base, a cyclization reaction is occurred to obtain 8-alkoxyimino-2,6-diazaspiro[3,4]octane derivative compound of formula 13. As a solvent for use in this reaction, acetonitrile, dimethylformamide, pyridine and toluene are preferred, and preferred base include organic bases such as triethylamine, diisopropylamine, pyridine, lutidine, *N,N*-dimethylaniline, *N,N*-dimethylaminopyridine, 1,8-diazabicyclo[5,4,0]undec-7-ene(DBU), 1,5-diazabicyclo[4,3,0]nonene-5(DBN) and 1,4-diazabicyclo[2,2,2]octane(DABCO). The amine protecting group P' in the compound of formula 13 is removed, according to the kind of amine protecting group, under the same condition as in the deprotection reaction of amine protecting group P, which reaction is used for the preparation of the compound of formula 1 from the compound of formula 4 as illustrated in Reaction scheme 2, to obtain the compound of formula 3 wherein R_3 is H. On the other hand, the compound of formula 3 wherein R_3 is C_{1-4} alkyl may be prepared by subjecting the exposed amine in the compound of formula 13 to a reductive alkylation reaction by using sodium cyanoborohydride as a reducing agent under a weak acidic condition with C_{1-4} aldehyde, and then removing amine protecting group P', according to the kind of amine protecting group, under the substantially same condition as in the deprotection reaction of amine protecting group P, which reaction

is used for the preparation of the compound of formula 1 from the compound of formula 4 as illustrated in Reaction scheme 2. Further, the compound of formula 3a, which is another starting material used in Reaction scheme 2 may be prepared by introducing an amine protecting group P, which is the same kind of protecting group as the previously defined amine protecting group P', into the compound of formula 13 to obtain the compound of formula 14 and, then, removing the amine protecting group P' in accordance with a suitable deprotection method selected from the previously presented deprotection methods depending on the kind of the amine protecting group.

The following Preparation Examples and Examples are intended to further illustrate the present invention without limiting its scope.

Preparation 1:

1-benzyl-4-methanesulfonyloxymethyl-4-hydroxymethyl-pyrrolidine-3-one-O-methyloxime

50g of 1-benzyl-4-ethoxycarbonyl-pyrrolidine-3-one was dissolved in 300ml of isopropanol and thereto 4ml of 10% NaOH and 20.7ml of formalin were added successively. The mixture was stirred for 30 minutes at room temperature and concentrated under the reduced pressure. 200ml of water was added to the concentrated residue. The resulting solution was extracted twice with each 200ml of ethylether, dried with magnesium sulfate, filtered and concentrated under the reduce pressure to give 46g of 1-benzyl-4-hydroxymethyl-4-ethoxycarbonyl-pyrroline-3-one(yield : 82.0%). The obtained compound was dissolved in 400ml of pyridine and thereto methoxylamine hydrochloride was added and stirred for 1 hour at room temperature. The reaction mixture was concentrated under the reduced pressure, diluted with 400ml of dichloromethane, washed with water and saline solution, dried with magnesium sulfate, filtered and concentrated under the reduced pressure to give 43g of 1-benzyl-4-hydroxymethyl-4-ethoxycarbonyl-pyrroline-3-one-O-methyloxi

me(yield : 84.6%). Thus obtained compound was dissolved in a solution of 22ml of triethylamine and 400ml of dichloromethane and cooled to 0-5℃ and thereto 10ml of methanesulfonylchloride was added dropwise and the reaction temperature was slowly increased up to room temperature. The reaction mixture was stirred for 1 hour, washed with water and saline solution, dried with magnesium sulfate, filtered and concentrated under the reduced pressure to give 50g of 1-benzyl-4-methanesulfonyloxymethyl-4-ethoxycarbonyl-pyrroline-3-one-O-methyloxime(yield : 92.6%). It was dissolved in 200ml of tetrahydrofuran and thereto 13g of sodium borohydride and 400ml of ethyl alcohol were added successively at room temperature and 11g of lithium chloride was added slowly. The reaction mixture was stirred for 5 hours and poured into 300ml of ice water. The resulting solution was adjusted to pH 5-6 with diluted hydrochloric acid, concentrated under the reduced pressure to remove most organic solvents therefrom, then extracted twice with each 200ml of ethylether, dried with magnesium sulfate, filtered and concentrated under the reduced pressure. The residue was purified by silicagel column chromatography(ethylacetate:normal hexane=2:1) to give 42g of the titled liquid compound(yield : 94.3%).

^{1}H-NMR($CDCl_3$, ppm): 2.54(d, 1H), 2.84(d, 1H), 2.96(s, 3H), 3.30(s, 2H), 3.60~3.71(m, 4H), 3.77(s, 3H), 4.32~4.53(m, 2H), 7.22~7.27(m, 5H).

Preparation 2:

1-benzyl-4-methanesulfonyloxymethyl-4-azidomethyl-pyrrolidine-3-one-O-methyloxime.

42g of 1-benzyl-4-methanesulfonyloxymethyl-4-hydroxymethyl-pyrrolidine-3-one-O-methyloxime was dissolved in 400ml of dimethylformamide and thereto 21g of sodium azide was added and the resulting solution was stirred for 6 hours at 110℃. The reaction mixture was concentrated under the reduce pressure, diluted with 300ml of ethylether, washed twice with each 200ml

of water and twice with each 200ml of saline solution, dried with magnesium sulfate, filtered and concentrated under the reduced pressure to give 31g of 1-benzyl-4-azidomethyl-4-hydroxymethyl-pyrrolidine-3-one-O-methyloxime (yield : 87.3%). The obtained compound and 18ml of triethylamine were added into 300ml of dichloromethane and cooled to 0-5℃, and thereto 9.0ml of methanesulfonylchloride was slowly added by dropping. The reaction temperature was increased up to room temperature and the mixture was stirred for 1 hour. The reaction mixture was washed with 200ml of water and 200ml of saline solution, dried with magnesium sulfate, filtered and concentrated under the reduced pressure and the concentrated residue was purified by silicagel column chromatography(ethylacetate:normal hexane=1:3) to give 38.8g of the titled compound(yield: 98.4%).

^{1}H-NMR($CDCl_3$, ppm): 2.77(d, 2H), 2.98(s, 3H), 3.34(s, 2H), 3.57(s, 2H), 3.65(s, 2H), 3.85(s, 3H), 4.31(s, 2H), 7.22~7.27(m, 5H).

Preparation 3:

t-butyl-6-benzyl-8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate.

10g of 1-benzyl-4-methanesulfonyloxymethyl-4-azidomethyl-pyrrolidine-3-one-O-methyloxime was dissolved in 100ml of ethyl acetate and thereto 5ml of 50% Raney nickel slurry was added and the resulting mixture was stirred for 3 hours under the pressure of hydrogen. The reaction mixture was filtered and concentrated under the reduced pressure to give 8.0g of 1-benzyl-4-methanesulfonyloxymethyl-4-aminomethyl-pyrrolidine-3-one-O-methyloxime(yield: 86%). The obtained compound was dissolved in 200ml of acetonitrile and thereto 3.9ml of 1,8-diazabicyclo[5,4,0]undec-7-ene was dropped, and the resulting mixture was stirred for 8 hours, concentrated under the reduce pressure, and dissolved in 150ml of dichloromethane, washed with 100ml of water and with 100ml of saline solution, dried with magnesium sulfate, filtered and concentrated under the reduced pressure to

give 4.0g of 6-benzyl-2,6-diazaspiro[3,4]octane-8-one-O-methyloxime(yield: 69.3%). The obtained compound and 2.5ml of triethylamine were dissolved in 50ml of dichloromethane and thereto 3.9g of di-t-butyldicarbonate. The resulting mixture was stirred for 4 hours, washed with 50ml of water, dried with magnesium sulfate, filtered and concentrated under the reduced pressure. The concentrated residue was purified by silicagel column chromatography(ethylacetate:normal hexane:dichloromethane=3:5:1) to give 4.6g of the titled compound(yield: 80.9%).

^{1}H-NMR($CDCl_3$, ppm): 1.36(s, 9H), 2.80(s, 2H), 3.24(s, 2H), 3.51(s, 2H), 3.78(d, 2H), 3.80(s, 3H), 4.24(d, 2H), 7.20~7.27(m, 5H).

Preparation 4:

t-butyl-8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate.

4.0g of t-butyl-6-benzyl-8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate was dissolved in 40ml of methanol and thereto 4.0g of 10% Pd-C was added. The resulting mixture was stirred for 2 hours under the pressure of hydrogen at 5℃, filtered and concentrated under the reduce pressure to give 1.3g of the titled compound(yield : 87.9%).

^{1}H-NMR($CDCl_3$, ppm): 1.39(s, 9H), 3.18(s, 2H), 3.58(s, 2H), 3.78(d, 2H), 3.80(s, 3H), 4.05(d, 2H).

Preparation 5:

1-benzyl-4-methanesulfonyloxymethyl-4-hydroxymethyl-pyrrolidine-3-one-O-ethyloxime.

The titled compound was prepared by the same procedure to Preparation 1.

^{1}H-NMR($CDCl_3$, ppm): 1.21(t, 3H, J=7.07Hz), 2.92(bs, 2H), 3.03(bs, 2H), 3.40(m, 2H), 3.72~3.75(m, 4H), 4.05~4.11(m, 2H), 4.35~4.42(m, 2H), 7.26~7.33(m, 5H).

Preparation 6:

1-benzyl-4-methanesulfonyloxymethyl-4-azidomethyl-pyrrolidine-3-one-O-ethyloxime.

The titled compound was prepared by the same procedure to Preparation 2.

^{1}H-NMR($CDCl_3$, ppm): 1.14(t, 3H, J=7.08Hz), 2.63~2.72(dd, 2H, J=9.48Hz), 2.91(s, 3H), 3.29(s, 2H), 3.51(s, 2H), 3.58(s, 2H), 4.04(q, 2H, J=7.08Hz), 4.28(s, 2H), 7.24(m, 5H).

Preparation 7:

t-butyl-6-benzyl-8-(ethoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate.

The titled compound was prepared by the same procedure to Preparation 3.

^{1}H-NMR($CDCl_3$, ppm): 1.19(m, 3H), 1.41(s, 9H), 2.85(bs, 2H), 3.30(bs, 2H), 3.64(bs, 2H), 3.80(bs, 2H), 4.07~4.11(m, 4H), 7.30(bs, 5H).

Preparation 8:

t-butyl-8-(ethoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate.

The titled compound was prepared by the same procedure to Preparation 4.

^{1}H-NMR($CDCl_3$, ppm): 1.20(t, 3H, J=6.84Hz), 1.38(s, 9H), 3.32(s, 2H), 3.62(s, 2H), 3.88(d, 2H), 4.10~4.19(m, 4H), 4.97(s, 1H).

Preparation 9:

6-benzyl-8-(methoxyimino)-2-methyl-2,6-diazaspiro[3,4]octane.

550mg of 6-benzyl-2,6-diazaspiro[3,4]octane-8-one-O-methyloxime was added to 10ml of ethanol and thereto 0.4ml of acetic acid and 176mg of

paraformaldehyde were added and the resulting mixture was stirred for 30 minutes at room temperature and thereto 370mg of sodium cyanoborohydride was added. The resulting mixture was stirred for 16 hours at room temperature, neutralized with aqueous solution of potassium carbonate and distilled under the reduced pressure and the obtained residue was added into 50ml of dichloromethane, washed with 50ml of water, dried with magnesium sulfate, filtered and concentrated under the reduced pressure. The residue was purified by silicagel column chromatography(methanol:normal hexane:dichloromethane=1:10:8) to give 350mg of the titled compound(yield: 60.1%).

^{1}H-NMR($CDCl_3$, ppm): 2.38(s, 3H), 2.87(s, 2H), 3.19(s, 2H), 3.23(d, 2H), 3.29(d, 2H), 3.58(s, 2H), 3.89(s, 3H), 7.17~7.27(m, 5H).

Preparation 10:

8-(methoxyimino)-2-methyl-2,6-diazaspiro[3,4]octane.

340mg of 6-benzyl-8-(methoxyimino)-2-methyl-2,6-diazaspiro[3,4]octane was dissolved in 10ml of methanol and thereto 300mg of 10% Pd-C was added. The resulting mixture was stirred for 2 hours at 50℃ under the pressure of hydrogen, filtered and concentrated under the reduced pressure to give 195mg of the titled compound(yield: 85.2%).

^{1}H-NMR($CDCl_3$, ppm): 2.33(s, 3H), 3.23~3.28(m, 4H), 3.35(d, 2H), 3.56(s, 2H), 3.86(s, 3H).

Preparation 11:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid.

400mg of 1-cyclopropyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid and 840mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate were added to

10ml of acetonitrile and the resulting mixture was stirred for 3 hours at 45-50℃. Then the precipitated solid was filtered and dried to give 650mg of the titled compound(yield:93.9%).

m.p. : 278-279℃

^{1}H-NMR($CDCl_3$, ppm): 1.05(m, 2H), 1.27(m, 2H), 1.45(s, 9H), 3.61~3.67(m, 1H), 3.90(s, 3H), 3.94(s, 2H), 4.25(s, 2H), 4.27(s, 2H), 4.56(s, 2H), 8.04(d, 1H, J=11.71Hz), 8.68(s, 1H).

Preparation 12:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

400mg of 1-cyclopropyl-6,7-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid and 840mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate were added to 10ml of acetonitrile and the resulting mixture was refluxed for 3 hours. Then the precipitated solid was filtered and dried to give 340mg of the titled compound(yield: 46.4%).

m.p. : 255~256℃

^{1}H-NMR($CDCl_3$, ppm): 1.18(bs, 2H), 1.39(m, 2H), 1.45(s, 9H), 3.52(bs, 1H), 3.91~4.05(m, 7H), 4.27(d, 2H), 4.34(s, 2H), 7.00(d, 1H, J=7.07Hz), 7.94(d, 1H, J=13.67Hz), 8.64(s, 1H).

Preparation 13:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

150mg of 1-cyclopropyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid and 320mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate were added to 10ml of acetonitrile and the resulting mixture was refluxed for 7 hours and

then cooled to room temperature. The precipitated solid was filtered and dried to give 120mg of the titled compound(yield: 55.5%).

m.p. : 255~256℃

^{1}H-NMR($CDCl_3$, ppm): 1.16(s, 2H), 1.29(d, 2H), 1.44(s, 9H), 3.92~3.94(m, 6H), 4.05(s, 2H), 4.22(d, 2H), 4.38(s, 2H), 7.89(d, 1H), 8.76(s, 1H).

Preparation 14:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-8-chloro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

300mg of 1-cyclopropyl-6,7-difluoro-8-chloro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid, 530mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate and 2g of Amberlite® IRA-420 were added to 10ml of acetonitrile and thereto 1ml of triethylamine was added by dropping. The resulting mixture was refluxed for 72 hours and then the resulting solid was filtered off. The filtrate was concentrated under the reduced pressure and thereto 10ml of ethylacetate was added and the resulting solution was stirred for 4 hours. The precipitated solid was filtered and dried to give 169mg of the titled compound(yield: 31.4%).

m.p. : 203~204℃

^{1}H-NMR($CDCl_3$, ppm): 1.16(bs, 2H), 1.39(d, 2H), 1,44(s, 9H), 3.92~3.94(m, 6H), 4.03(s, 2H), 4.21(d, 2H), 4.38(s, 2H), 7.88(d, 1H, J=13.19Hz), 8.76(s, H).

Preparation 15:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-5-amino-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

750mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinoline-

carboxylic acid, 1.05g of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate and 4g of Amberlite® IRA-420 were added to 20ml of acetonitrile and thereto 2ml of triethylamine was added by dropping. The mixture was refluxed for 5 days and then 2ml of dimethylformamide was added thereto. The resulting mixture was stirred for 1 hour and thus precipitated solid was filtered off. The filtrate was concentrated under the reduced pressure and then to the resulting residue 10ml of acetonitrile was added and stirred for 1 hour. The precipitated solid was filtered and dried to give 420mg of the titled compound(yield: 30.9%).

m.p. : 256~257℃

1H-NMR($CDCl_3$, ppm): 1.05(s, 2H), 1.18(d, 2H), 1,44(s, 9H), 3.89~3.96(m, 6H), 3.99(s, 2H), 4.21(d, 2H), 4.34(s, 2H), 8.62(s, 1H).

Preparation 16:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

95mg of 1-(2,4-difluorophenyl)-6,7-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid, 120mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate and 400mg of Amberlite® IRA-420 were added to 10ml of acetonitrile and thereto 0.5ml of triethylamine was added by dropping. The resulting mixture was refluxed for 48 hours and thus precipitated solid was filtered off. To the filtrate 5ml of ethylether was added and the resulting mixture was stirred for 4 hours. The precipitated solid was filtered and dried to give 110mg of the titled compound(yield: 67.8%).

m.p. : 263~264℃

^{1}H-NMR($CDCl_3$, ppm): 1,43(s, 9H), 3.64(s, 2H), 3.86~3.91(m, 2H), 3.92(s, 3H), 4.18~4.21(m, 4H), 5.91(d, 1H, J=6.84Hz), 7.18~7.24(m, 2H), 7.48(m, 1H), 8.06(d, 1H, J=13.68), 8.54(s, 1H).

Preparation 17:

7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid.

110mg of 1-(2,4-difluorophenyl)-6-fluoro-7-chloro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 120mg of t-butyl 8-(methoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate were added to 10ml of acetonitrile and thereto 0.5ml of triethylamine was added dropwise. The resulting mixture was stirred for 4 hours at 50℃ and then for 2 hours at the room temperature. The precipitated solid was filtered and dried to give 150mg of the titled compound(yield: 79.9%).

m.p. : 230~232℃

^{1}H-NMR($CDCl_3$, ppm): 1.47(s, 9H), 3.82~3.92(m, 7H), 4.17~4.29(m, 4H), 7.07~7.13(m, 2H), 7.35~7.41(m, 1H), 8.12(d, 1H, J=12.20Hz), 8.64(s, 1H).

Preparation 18:

7-[2-(t-butoxycarbonyl)-8-(ethoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid.

360mg of 1-cyclopropyl-6-fluoro-7-chloro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid and 500mg of t-butyl 8-(ethoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate were added to 10ml of acetonitrile and thereto 1ml of triethylamine was added by dropping. The resulting mixture was stirred for 2 hours at 50℃ and then for 1 hour at the room temperature. The precipitated solid was filtered and dried to give 380mg of the titled compound(yield: 57.9%).

m.p. : 261~262℃

^{1}H-NMR($CDCl_3$, ppm): 1.06(s, 2H), 1.27~1.31(m, 5H), 1.45(s, 9H), 3.64~3.66(m, 1H), 3.96(d, 2H), 4.19~4.28(m, 6H), 4.57(s, 2H), 8.08(d, 1H, J=12.20Hz), 8.12(s, 1H).

Preparation 19:

7-[2-(t-butoxycarbonyl)-8-(ethoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-5-amino-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid.

400mg of 1-cyclopropyl-5-amino-6,7,8-trifluoro-4-oxo-1,4-dihydro-3-quinoline-carboxylic acid, 680mg of t-butyl 8-(ethoxyimino)-2,6-diazaspiro[3,4]octane-2-carboxylate and 2g of Amberlite® IRA-420 were added to 15ml of acetonitrile and thereto 1.5ml of triethylamine was dropped and the resulting mixture was refluxed for 5 days and filtered. The filtrate was concentrated under the reduced pressure and to the resulting residue 10ml of isopropanol was added and the resulting solution was stirred for 1 hour at room temperature. The precipitated solid was filtered and dried to give 380mg of the titled compound(yield: 51.1%).

m.p. : 235~236℃

1H-NMR(CDCl3, ppm): 0.98(bs, 2H), 1.15~1.23(m, 5H), 1.34(s, 9H), 3.26~3.30(m, 1H), 3.86(d, 2H), 3.93(s, 2H), 4.06~4.12(m, 4H), 4.28(s, 2H), 8.53(s, 1H).

Example 1.

1-Cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid methanesulfonate

350mg of 7-[2-(t-buthoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3.4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid

was dissolved in 5ml of dichloromethane and thereto 0.6ml of trifluoroacetic acid was dropped. The mixture was stirred for 5 hours at room temperature and thereto 10ml of ethylether was added. It was stirred additionally for 1 hour and thus precipitated solid was filtered, dissolved in 5ml of diluted NaOH and neutralized with diluted hydrochloric acid. The precipitate thus obtained was filtered and dried. The resulting solid was added to 5ml of 1N-methanesulfonic acid in ethanol and stirred for 1 hour. Thus obtained precipitate was filtered and dried to give 185g of the titled compound(yield : 47.8%).

m.p. : 228~229℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 0.97(s, 2H), 1.14(d, 2H), 2.48(s, 3H), 3.57(bs, 1H), 3.88(s, 3H), 4.06~4.17(m, 4H), 4.40(s, 2H), 4.49(s, 2H), 7.88(d, 1H, J=12.67Hz), 8.49(s, 1H).

Example 2.

1-Cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid methanesulfonate

175mg of 7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolincarboxylic acid was dissolved in 5ml of dichloromethane and thereto 1ml of trifluoroacetic acid was added by dropping. The resulting mixture was stirred at room temperature for 18 hours, and thereto 10ml of ethylether was added. The resulting precipitate was filtered and dried. Thus obtained solid was dissolved in 2ml of diluted NaOH and neutralized with diluted hydrochloric acid, and the resulting precipitate was filtered and dried. The solid thus obtained was added to 2ml of 1N-methanesulfonic acid in ethanol and stirred at room temperature for 3 hours. The precipitate was filtered and dried to give 35mg of the titled compound(yield : 28.5%).

m.p. : 216~217℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 1.04(s, 2H), 1.22(d, 2H), 2.45(s, 3H),

3.62(bs, 1H), 3.84(s, 3H), 4.06~4.18(m, 6H), 4.23(s, 2H), 7.10(d, 1H, J=7.15Hz), 7.76(d, 1H, J=14.27Hz), 8.52(s, 1H).

Example 3.

1-Cyclopropyl-6,8-difluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid

150mg of 7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was dissolved in 5ml of dichloromethane and thereto 1ml of trifluoroacetic acid was added dropwise. The mixture was stirred for 5 hours at room temperature and thereto 10ml of ethylether was added. It was additionally stirred for 1 hour, and thus precipitated solid was filtered and dried. Thus obtained solid was dissolved in 5ml of diluted sodium hydroxide and neutralized with diluted hydrochloric acid. The resulting precipitate was filtered and dried to give 115mg of the titled compound(yield : 87.4%).

m.p. : 205~207℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 1.16(s, 4H), 3.87~3.97(m, 4H), 4.06~4.33(m, 6H), 4.39(s, 2H), 7.77(d, 1H, J=13.15Hz), 8.63(s, 1H).

Example 4

1-Cyclopropyl-6-fluoro-8-chloro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid

150mg of 7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-8-chloro-4-oxo-1,4-dihydro-3-quinolinecaboxylic acid was dissolved in 5ml of dichloromethane and thereto 0.2ml of trifluoroacetic acid was added dropwise. The mixture was stirred for 18 hours at room temperature, and thereto 10ml of pyridine and 10ml of water were added. It was distilled under the reduced pressure to remove

dichloromethane and stirred for 1 hour. The precipitated solid was filtered and dried to give the titled compound(67mg).

yield : 54.7%

m.p. : 220~221℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 0.95(s, 2H), 1.16(d, 2H), 3.89(s, 3H), 4.02~4.06(m, 4H), 4.13~4.23(m, 4H), 4.34(bs, 1H), 7.92(d, 1H, J=12.44Hz), 8.82(s, 1H).

Example 5

1-Cyclopropyl-5-amino-6,8-difluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid methanesulfonate

420mg of 7-[2-(t-Butoxycabonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-5-amino-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was dissolved in 10ml of dichloromethane and thereto 1ml of trifluoroacetic acid was added dropwise. The mixture was stirred at room temperature for 18 hours, and thereto 10ml of pyridine was added. It was distilled under the reduced pressure. The residue was purified by silica gel chromatography(chloroform:methyl alcohol:water=6:2:0.2). Thus obtained solid was added to 2ml of 1N-methansulfonic acid in ethanol, stirred for 3 hours at room temperature. The precipitated solid was filtered and dried to give the titled compound(165mg)

yield : 39.6%

m.p. : 238~239℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 1.09(bs, 4H), 2.49(s, 3H), 3.89(s, 3H), 3.92~3.99(m, 1H), 4.08~4.20(m, 6H), 4.35(s, 2H), 8.50(s, 1H).

Exmaple 6

1-(2,4-Difluorophenyl)-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid dimethanesulfonate

90mg of 7-[2-(t-butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was dissolved in 5ml of dichloromethane and thereto 0.1ml of trifluoroacetic acid was added by dropping. The mixture was stirred at room temperature for 12 hours and thereto 5ml of pyridine was added. The mixture was distilled under the reduced pressure to remove dichloromethane and thereto 5ml of water was added. It was stirred at room temperature for 2 hours. The resulting precipitate was filtered and dried, and added to 2ml of 1N-methansulfonic acid in ethanol and stirred at room temperature for 1 hour. Thus precipitated solid was filtered and dried to give the titled compound(45mg).

yield : 43.1%

m.p. : 216~217℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 2.49(s, 6H), 3.74~4.09(m, 11H), 5.93(d, 1H), 7.24(m, 1H), 7.45(m, 1H), 7.88(m, 1H), 7.89(d, 1H, J=14.40Hz), 8.60(s, 1H).

Example 7

1-(2,4-Difluorophenyl)-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

140mg of 7-[2-(t-Butoxycarbonyl)-8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was dissolved in 5ml of dichloromethane and thereto 0.2ml of trifluoroacetic acid was added by dropping. The mixture was stirred at room temperature for 12 hours and thereto 5ml of pyridine was added. It was distilled under the reduced pressure to remove dichloromethane and thereto 5ml of water was added. It was stirred at room temperature for 2 hours. The resulting precipitate was filtered and dried. Thus obtained solid

was added to 2ml of 1N-methansulfonic acid in ethanol and stirred at room temperature for 1 hour. The precipitate was filtered and dried to give the titled compound(95mg).

yield : 68.3%

m.p. : 201~202℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 2.49(s, 3H), 3.85(s, 3H), 3.88~4.10(m, 8H), 7.23~7.26(m, 1H), 7.40~7.46(m, 1H), 7.70~7.76(m, 1H), 8.07(d, 1H, J=12.44Hz), 8.76(s, 1H).

Example 8

1-Cyclopropyl-6-fluoro-7-[8-(ethoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid methanesulfonate

380mg of 7-[2-(t-Butoxycarbonyl)-8-(ethoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was dissolved in 5ml of dichloromethane and thereto 0.6ml of trifluoroacetic acid was added dropwise. The mixture was stirred at room temperature for 12 hours and thereto 3ml of pyridine was added. It was distilled under the reduced pressure to remove dichloromethane and 1ml of water was added thereto. It was stirred at room temperature for 2 hours. Thus precipitated solid was filtered and dried. The resulting solid was added to 2ml of 1N-methansulfonic acid in ethanol and stirred at room temperature for 1 hour. The precipitate was filtered and dried to give 220mg of the titled compound(yield : 58.3%).

m.p. : 211~212℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 1.02(bs, 2H), 1.19~1.28(m, 5H), 2.48(s, 3H), 3.63~3.68(m, 1H), 4.06~4.20(m, 5H), 4.38(s, 2H), 4.51(s, 2H), 7.97(d, 1H, J=12.44Hz), 8.55(s, 1H).

Example 9

1-Cyclopropyl-5-amino-6,8-difluoro-7-[8-(ethoxyimino)-2,6-diazaspiro[3,4]

oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid methanesulfonate

380mg of 7-[2-(t-Butoxycabonyl)-8-(ethoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-1-cyclopropyl-5-amino-6,8-difluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was dissolved in 10ml of dichloromethane and thereto 0.7ml of trifluoroacetic acid was dropped. The mixture was stirred at room temperature for 18 hours and thereto 10ml of pyridine was added. It was distilled under the reduced pressure to remove the solvent. The residue was purified by silica gel chromatography(chloroform : methyl alcohol: water = 6 : 2 : 0.2). Thus obtained solid was added to 1.5ml of 1N-methansulfonic acid in ethanol and stirred at room temperature for 3 hours. The resulting precipitate was filtered and dried to give 180mg of the titled compound(yield : 47.1%).

m.p. : 221~222℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 0.96~1.02(m, 4H), 1.15(t, 3H, J=7.08Hz), 2.49(s, 3H), 3.87(d, 1H), 3.98~4.12(m, 8H), 4.22(s, 2H), 8.42(s, 1H).

Example 10

1-Cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

300mg of 1-Cyclopropyl-6-fluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid was added to 10ml of ethanol, and thereto 0.2ml of acetic acid was dropped and 42mg of p-formaldehyde was added. The mixture was stirred at room temperature for 30 minutes, and thereto 85mg of sodium cyanoborohydride was added. It was stirred at room temperature for 2 hours. The resulting precipitate was filtered and dried to give 260mg of the titled compound(yield : 83.7%).

m.p. : 225~227℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 0.95(s, 2H), 1.16(d, 2H), 2.49(s, 3H), 3.58~3.61(m, 1H), 3.87(s, 3H), 4.08~4.18(m, 4H), 4.34(s, 2H), 4.46(s, 2H), 7.93(d, 1H, J=12.43Hz), 8.51(s, 1H).

Example 11

1-Cyclopropyl-5-amino-6,8-difluoro-7-[8-(methoxyimino)-2-methyl-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid

300mg of 1-Cyclopropyl-5-amino-6,8-difluoro-7-[8-(methoxyimino)-2,6-diazaspiro[3,4]oct-6-yl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid was added to 10ml of ethanol, and thereto 0.2ml of acetic acid was dropped and 44mg of p-formaldehyde was added. It was stirred at room temperature for 30 minutes and thereto 91mg of sodium cyanoborohydride was added. It was stirred at room temperature for 2 hours. The resulting precipitate was filtered to give 280mg of the titled compound(yield : 90.4%).

m.p. : 220~222℃

^{1}H-NMR(DMSO-d_6+CF_3COOD, ppm): 1.15~1.23(m, 4H), 2.64(s, 3H), 4.05(s, 3H), 4.06~4.10(m, 1H), 4.20~4.39(m, 6H), 4.47(s, 2H), 8.62(s, 1H).

Experimental 1. In vitro Antibacterial Activity Test

In order to evaluate the in vitro antibacterial activities of the compounds prepared in examples according to the present invention the minimum inhibitory concentrations(MIC, μg/ml) were measured by the 2-fold agar dilution method(Hoechst 345) using the Muller-Hinton agar. 10^7 cfu/ml of bacteria were inoculated and cultured for 18 hours at 37℃ and then the antibacterial activities were measured. For the methicillin resistant strains the activities were measured after 48 hours of cultivation at 30℃. Hoechst Standard strains were used for the testings.

The result is shown in the next tables 1 and 2.

Table 1. In vitro Antibacterial Activity (μg/ml)

Strains \ Compounds	Example 1	Example 2	Example 3	Example 4
Streptococcus pyogens 308A	0.098	0.195	0.391	0.195
Streptococcus pyogens 77A	0.007	0.007	0.025	0.013
Streptococcus faecium MD 8b	0.049	0.098	0.098	0.098
Staphylococcus aureus SG511	0.007	0.013	0.025	0.013
Staphylococcus aureus 285	0.025	0.049	0.049	0.049
Staphylococcus aureus 503	0.025	0.049	0.098	0.025
Esherichia coli 078	0.013	0.025	0.098	0.025
Esherichia coli DC0	0.195	0.198	0.391	0.391
Esherichia coli DC2	0.025	0.013	0.025	0.049
Esherichia coli TEM	0.025	0.049	0.049	0.049
Esherichia coli 1507E	0.025	0.049	0.049	0.049
Pseudomonas aeruginosa 9027	0.781	0.781	1.563	0.781
Pseudomonas aeruginosa 1592E	0.391	0.391	0.781	0.781
Pseudomonas aeruginosa 1771	0.391	0.391	1.563	0.781
Pseudomonas aeruginosa 1771M	0.391	0.391	0.781	0.391
Salmonella typhimurium	0.013	0.025	0.025	0.025
Klebsiella oxytoca 1082E	0.004	0.007	0.007	0.004
Klebsiella aerogenes 1522E	0.049	0.098	0.098	0.098
Enterobacter clocae P99	0.025	0.049	0.049	0.049
Enterobacter clocae 1321E	0.013	0.025	0.025	0.025

(μg/ml)

Strains \ Compounds	Example 5	Example 6	Example 77	Example 8
Streptococcus pyogens 308A	0.025	0.195	0.195	0.098
Streptococcus pyogens 77A	<0.002	0.013	0.013	0.007
Streptococcus faecium MD 8b	0.025	0.195	0.098	0.098
Staphylococcus aureus SG511	<0.002	0.049	0.013	0.007
Staphylococcus aureus 285	0.007	0.098	0.049	0.025
Staphylococcus aureus 503	<0.002	0.049	0.025	0.013
Esherichia coli 078	<0.002	0.049	0.049	0.013
Esherichia coli DC0	0.098	0.781	0.781	0.391
Esherichia coli DC2	0.013	0.098	0.098	0.025
Esherichia coli TEM	0.013	0.195	0.098	0.025
Esherichia coli 1507E	0.007	0.195	0.195	0.049
Pseudomonas aeruginosa 9027	0.781	3.125	1.563	1.563
Pseudomonas aeruginosa 1592E	0.391	1.563	1.563	0.781
Pseudomonas aeruginosa 1771	0.391	1.563	1.563	0.781
Pseudomonas aeruginosa 1771M	0.195	1.563	0.781	0.781
Salmonella typhimurium	<0.002	0.049	0.049	0.013
Klebsiella oxytoca 1082E	<0.002	0.013	0.013	0.004
Klebsiella aerogenes 1522E	0.025	0.391	0.195	0.098
Enterobacter clocae P99	0.007	0.098	0.098	0.025
Enterobacter clocae 1321E	0.004	0.098	0.049	0.025

(μg/ml)

Strains \ Compounds	Example 9	Example 10	Example 11	Ciproflo xacin	Sparflox acin
Streptococcus pyogens 308A	0.025	0.098	0.013	3.125	0.391
Streptococcus pyogens 77A	0.004	0.013	0.004	0.781	0.195
Streptococcus faecium MD 8b	0.049	0.098	0.049	0.391	0.391
Staphylococcus aureus SG511	<0.002	0.013	<0.002	0.195	0.098
Staphylococcus aureus 285	0.007	0.049	0.007	0.781	0.049
Staphylococcus aureus 503	<0.002	0.025	0.004	0.391	0.049
Esherichia coli 078	0.004	0.013	<0.002	0.004	0.004
Esherichia coli DC0	0.195	0.391	0.098	0.195	0.195
Esherichia coli DC2	0.013	0.049	0.013	0.049	0.025
Esherichia coli TEM	0.013	0.049	0.013	0.007	0.013
Esherichia coli 1507E	0.013	0.049	0.013	0.007	0.025
Pseudomonas aeruginosa 9027	0.781	0.781	0.781	0.195	0.781
Pseudomonas aeruginosa 1592E	0.781	0.781	0.781	0.195	0.781
Pseudomonas aeruginosa 1771	0.781	0.781	0.781	0.195	0.781
Pseudomonas aeruginosa 1771M	0.391	0.781	0.391	0.049	0.195
Salmonella typhimurium	0.007	0.049	0.007	0.007	0.007
Klebsiella oxytoca 1082E	<0.002	0.007	<0.002	<0.002	<0.002
Klebsiella aerogenes 1522E	0.049	0.098	0.049	0.013	0.025
Enterobacter clocae P99	0.007	0.049	0.013	0.007	0.007
Enterobacter clocae 1321E	0.007	0.025	0.004	<0.002	0.004

Table 2. In vitro Antibacterial Activity against resistant strains.

(μg/ml)

Strains \ Compounds	Example 1	Example 5	Example 9	Example 11	Ciproflox acin	Sparflox acin
Staphylococcus aureus 88E	0.049	0.007	0.007	0.007	0.781	0.098
Staphylococcus aureus 121E	0.049	0.013	0.013	0.013	0.781	0.098
Staphylococcus aureus 208E	0.049	0.007	0.013	0.013	0.781	0.098
Staphylococcus aureus 256E	0.025	0.007	0.013	0.007	0.781	0.098
Staphylococcus aureus 690E	0.025	0.007	0.007	0.007	0.391	0.049
Staphylococcus aureus 692E	0.025	0.004	0.007	0.007	0.391	0.049
Staphylococcus aureus 693E	0.049	0.007	0.013	0.013	0.391	0.049
Staphylococcus aureus 694E	0.049	0.007	0.013	0.013	0.391	0.098
Staphylococcus aureus 695E	0.049	0.007	0.013	0.013	0.391	0.049
Staphylococcus aureus 697E	0.013	<0.002	0.004	0.004	0.391	0.049
Staphylococcus aureus 701E	0.049	0.007	0.013	0.013	0.391	0.098
Staphylococcus aureus 703E	0.049	0.007	0.013	0.013	0.391	0.098
Staphylococcus aureus 179	0.781	0.098	0.098	0.195	12.500	6.250
Staphylococcus aureus 241	0.781	0.098	0.098	0.195	12.500	6.250
Staphylococcus aureus 293	0.781	0.098	0.098	0.195	12.500	6.250
Staphylococcus aureus 303	0.781	0.098	0.098	0.195	12.500	3.125
Staphylococcus aureus 8236	0.781	0.098	0.098	0.195	12.500	6.250
Staphylococcus epidermidis 178	1.563	0.391	0.391	0.781	50.000	6.250
Staphylococcus epidermidis 291	1.563	0.391	0.391	0.781	50.000	6.250

Experimental 2. Acute Toxicity Test.

In the acute toxicity test of the quinolonecarboxylic acid derivatives prepared in examples according to the present invention ICR mice of 23-25g were used. Each group of mice comprised 5 male and 5 female mice and each sample compound was distributed into 5 doses.

After mice were starved for 24 hours only with water, samples diluted in 0.2ml of 0.1N NaOH and respectively adjusted to a predetermined dose were injected into the vein of mouse tails. After 1 hour from the injection mice was fed and then during 14 days lethality was observed.

As the result, the values of LD_{50}(mg/kg) of quinolonecarboxylic acid derivatives and its pharmaceutically acceptable salts according to the invention were of over 320, whereby it was proved that the compounds of the invention have high safety as antibacterial agents.

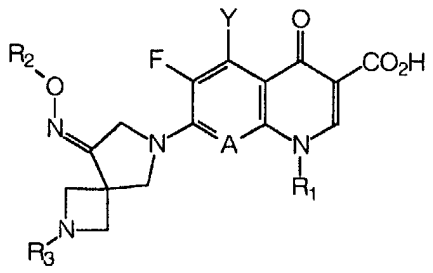
Effect of the invention

The quinolonecarboxylic acid derivatives according to the present invention are very safe compounds as having very low toxicity, and they have more improved antibacterial activity than that of known quinolone antibacterial agents against gram positive bacteria, good antibacterial activity against gram negative bacteria and especially excellent antibacterial activity against methicillin resistant bacteria and known quinolone resistant bacteria.

Accordingly, the quinolonecarboxylic acid derivatives of the present invention are very useful as antibacterial agents.

What is claimed is:

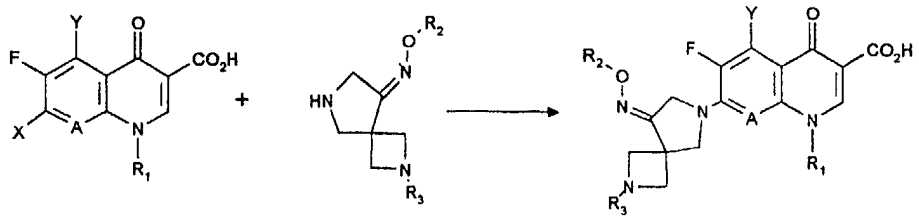
1. A quinolonecarboxylic acid derivative represented by following formula 1, or a pharmaceutically acceptable salt or an isomer thereof:



1

Wherein, A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; and R_3 is H or C_{1-4} alkyl.

2. A process for preparing a quinolonecarboxylic acid derivative, which comprises conducting coupling reaction of the compound of formula 2 with the compound of formula 3 under the presence of an acid acceptor to obtain the compound of formula 1:

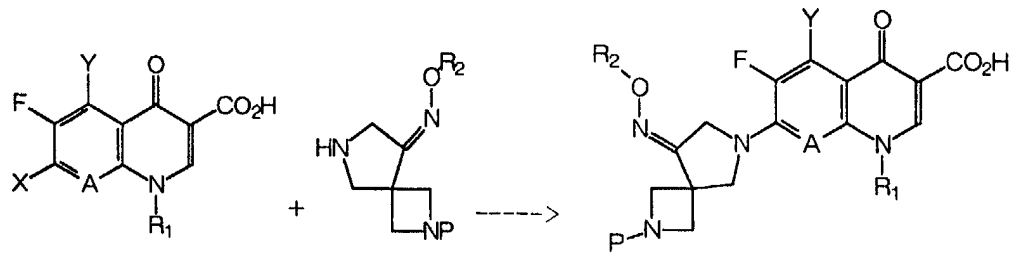


2 3 1

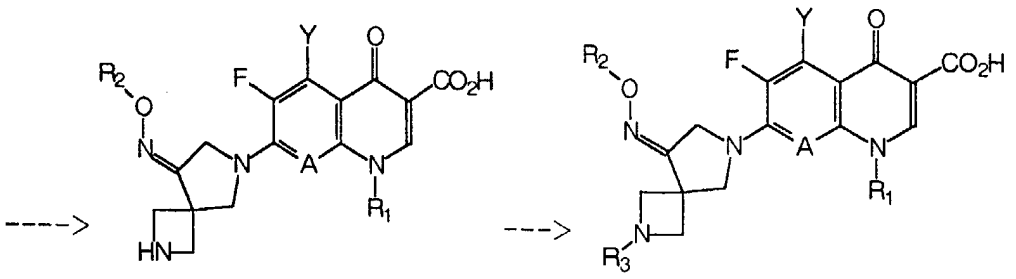
Wherein, A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; R_3 is H or C_{1-4} alkyl; and X is a halogen atom.

3. The process of claim 2, wherein an ion-exchange resin selected from the group consisting of Amberlite® IRA-420, Amberlite® IRA-900 and Amberlite® IRA-64 is used for increasing the reactivity of the condensation reaction.

4. A process for preparing a quinolonecarboxylic acid derivative, which comprises conducting coupling reaction of the compound of formula 2 with the compound of formula 3a under the presence of an acid acceptor to obtain the compound of formula 4, and removing the amine protecting group(P) from the compound of formula 4 to obtain the compound of formula 1 wherein R_3 is H, said process optionally further comprising subjecting the compound of formula 1 wherein R_3 is H to a reductive alkylation reaction using C_{1-4} aldehyde to obtain a compound of formula 1 wherein R_3 is C_{1-4} alkyl:



2 3a 4

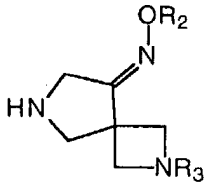


1 (R_3=H) 1 (R_3=C_{1-4} alkyl)

Wherein, A is C-H, C-F, C-Cl, C-O-CH_3 or N; Y is H or amino; R_1 is cyclopropyl or 2,4-difluorophenyl; R_2 is C_{1-4} alkyl; R_3 is H or C_{1-4}

alkyl; X is a halogen atom; and P is an amine protecting group.

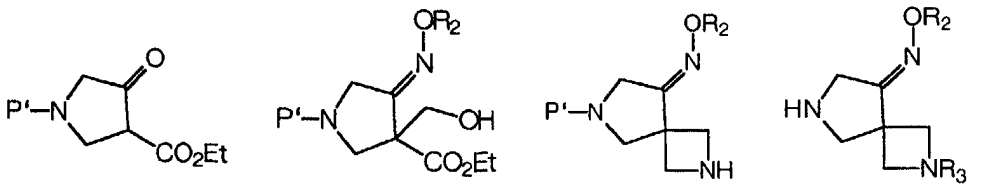
5. A 8-alkoxyimino-2,6-diazaspiro[3,4]octane derivative of formula 3:



3

Wherein, R_2 is C_{1-4} alkyl, and R_3 is H or C_{1-4} alkyl.

6. A process for preparing the compound of formula 3, which comprises converting the compound of formula 5 to an oxime compound of formula 7, subjecting the oxime compound to cyclization reaction to obtain the compound of formula 13 and subjecting the compound of formula 13 to deprotection reaction, or a reductive alkylation reaction with a lower aldehyde followed by a deprotection reaction to obtain the compound of formula 3:

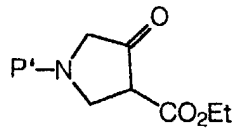


5 7 13 3

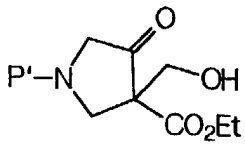
Wherein, R_2 is C_{1-4} alkyl; R_3 is H or C_{1-4} alkyl; and P' is an amino protecting group.

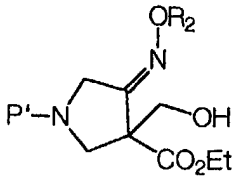
7. The process of claim 6, wherein the compound of formula 5 is converted to an oxime compound by reacting it with formaldehyde to obtain the compound of formula 6 and then reacting the compound of formula 6 with alkoxylamine to obtain the alkoxyimino compound of

formula 7:



5

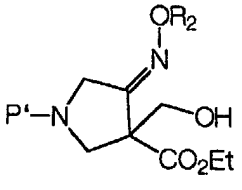


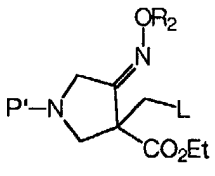


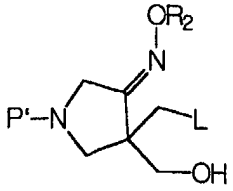
5 6 7

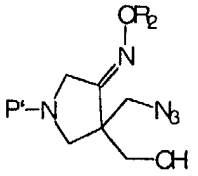
Wherein, R_2 is C_{1-4} alkyl; and P' is an amino protecting group.

8. The process of claim 6, wherein the cyclization reaction comprises: converting the hydroxy group(-OH) in the compound of formula 7 to leaving group L selected from the group consisting of methansulfonyloxy, p-toluenesulfonyloxy and halogen to obtain the compound of formula 8; reducing an ester group in the compound of formula 8 to an alcohol to obtain an alcohol compound of formula 9; substituting the leaving group L in the compound of formula 9 with an azido group to obtain the compound of formula 10; converting an hydroxy group in the compound of formula 10 to leaving group L to obtain the compound of formula 11; reducing an azido group in the compound of formula 11 to a primary amine to obtain the compound of formula 12; and subjecting the compound of formula 12 to a cyclization reaction to obtain the compound of formula 13:

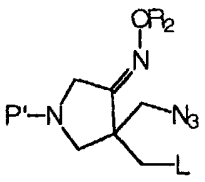




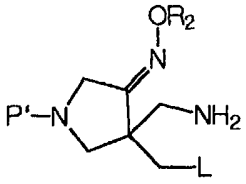




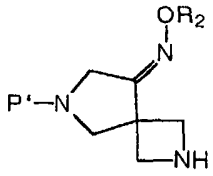
7 8 9 10



11



12



13

Wherein, R_2 is C_{1-4} alkyl; and P' is an amino protecting group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00185

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 487/10; A 61 K 31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 487/00; A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPIL database, Derwent Publ. Ltd., London (GB)
Questel database, file CA; Questel.Orbit Imagination (ed. 1995)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 722 941 A2 (ELI LILLY AND COMPANY) 24 July 1996 (24.07.96), totality.	1-8
A	Database WPIL on Questel, week 9519, Derwent Publi- cations Ltd., AN 95-144821, JP 707110 A (HOKURIKU PHARM. CO. LTD.), abstract.	1-8
A	EP 0 643 058 A1 (DAIICHI PHARMACEUTICAL CO.) 15 March 1995 (15.03.95), totality.	1-8
A	EP 0 550 025 A1 (KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY) 07 July 1993 (07.07.93), totality.	1-8
A	Database WPIL on Questel, week 9412, Derwent Publi- cations Ltd., AN 94-097812, JP 6049060 A (HOKURIKU PHARM. CO. LTD.), abstract.	1-8
A	Database WPIL on Questel, week 9412, Derwent Publi- cations Ltd., AN 94-097811, JP 6049059 A (HOKURIKU PHARM.. CO. LTD.), abstract.	1-8
A	Database WPIL on Questel, week 9433, Derwent Publi- cations Ltd., AN 94-269425, JP 6199834 A (HOKURIKU	1-8

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1998 (15.09.98)	30 September 1998 (30.09.98)
Name and mailing address of the ISA/ Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Weniger Telephone No. 1/53424/341

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00185

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	PHARM. CO. LTD.), abstract.	
A	EP 0 357 047 B1 (DAIICHI SEIYAKU CO.) 07 March 1990 (07.03.90), totality.	1-8
A	US 4 638 067 A (TOWNLEY P. CULBERTSON et al.) 20 January 1987 (20.01.87), totality.	1-8
A	EP 0 153 165 A2 (WARNER LAMBERT COMPANY) 28 August 1985 (28.08.85), totality.	1-8
A	EP 0 529 688 A2 (DAIICHI PHARMACEUTICAL CO.) 03 March 1993 (03.03.93), totality.	6-8

Form PCT/ISA/210 (continuation of second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00185

Im Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
EP A2 722941	24-07-96	AU A1 46516/96	07-08-96
		BR A 9607077	18-11-97
		CA AA 2210220	25-07-96
		CZ A3 9702207	18-02-98
		FI A 973024	16-07-97
		FI A0 973024	16-07-97
		NO A0 973281	15-07-97
		NO A 973281	08-09-97
		PL A1 321851	22-12-97
		US A 5576321	19-11-96
		WO A1 9622290	25-07-96
		US A 5614523	25-03-97
		US A 5627196	06-05-97
		US A 5741789	21-04-98
		US A 5789402	04-08-98
EP A1 643058	15-03-95	AU A1 72862/94	23-03-95
		AU B2 679094	19-06-97
		BG A 99035	31-05-95
		CA AA 2131761	11-03-95
		CN A 1106006	02-08-95
		CZ A3 9402176	15-03-95
		FI A0 944174	09-09-94
		FI A 944174	11-03-95
		HR A1 940506	30-04-97
		HU A0 9402597	28-11-94
		HU A2 68541	28-06-95
		IL A0 110909	28-11-94
		JP A2 7126266	16-05-95
		LV A 11322	20-06-96
		LV B 11322	20-10-96
		NO A0 943313	08-09-94
		NO A 943313	13-03-95
		NZ A 264422	26-07-95
		PL A1 304989	20-03-95
		SI A 9400349	30-04-95
		SK A3 1076/94	10-05-95
		US A 5693814	02-12-97
		ZA A 9406853	24-04-95
EP A1 550025	07-07-93	KR B1 9611370	22-08-96
EP B1 357047	03-11-93	AT E 96791	15-11-93
		AT E 160141	15-11-97
		AU A1 41006/89	08-03-90
		AU B2 619891	06-02-92
		CA A1 1336090	27-06-95
		CN A 1040790	28-03-90
		CN A 1100095	15-03-95
		CN B 1028102	05-04-95
		CN B 1036193	22-10-97
		DE C0 68910441	09-12-93
		DE T2 68910441	03-03-94
		DE C0 68928447	18-12-97
		DE T2 68928447	18-06-98
		DK A0 4262/89	30-08-89
		DK A 4262/89	01-03-90
		EP A1 357047	07-03-90
		EP A2 529688	03-03-93
		EP A3 529688	10-03-93
		EP B1 529688	12-11-97
		ES T3 2061845	16-12-94
		ES T3 2111029	01-03-98
		FI A0 894045	29-08-89
		FI A 894045	01-03-90
		FI A 934016	14-09-93
		FI A0 934016	14-09-93
		FI B 92703	15-09-94
		FI C 92703	27-12-94
		IE B 63492	03-05-95
		IL A0 91474	29-04-90
		IL A1 91474	30-05-94
		IN A 170262	07-03-92
		JP A2 8333337	17-12-96
		NO A0 893453	29-08-89
		NO A 893453	01-03-90
		NO B 177638	17-07-95
		NO C 177638	25-10-95
		NZ A 230484	25-06-91

Form PCT/ISA/210 (patent family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00185

			PT	A	91602	08-03-90
			PT	B	91602	31-05-95
			US	A	5286723	15-02-94
			US	A	5508428	16-04-96
			JP	A2	3095176	19-04-91
			HR	A1	930082	30-04-96
			SI	A	8911674	31-10-97
			YU	A	167489	30-04-91
			RU	C1	2094432	27-10-97
			ZA	A	8906607	27-03-91
US A	4638067	20-01-87	AT	E	35987	15-08-88
			AU	A1	18698/83	15-03-84
			AU	B2	562286	04-06-87
			CS	B2	246065	16-10-86
			DD	A5	216010	28-11-84
			DE	C0	3377493	01-09-88
			DK	A0	4074/83	05-09-83
			DK	A	4074/83	10-03-84
			DK	A	700/94	16-06-94
			DK	B1	170471	11-09-95
			DK	B1	171098	03-06-96
			EP	A2	106489	25-04-84
			EP	A3	106489	24-04-85
			EP	B1	106489	27-07-88
			ES	A1	525493	16-01-85
			ES	A5	525493	11-02-85
			ES	A1	8502687	16-04-85
			ES	A1	529934	01-06-85
			ES	A1	529936	16-06-85
			ES	A1	529937	16-06-85
			ES	A5	529934	28-06-85
			ES	A1	529935	01-07-85
			ES	A5	529936	16-07-85
			ES	A5	529937	16-07-85
			ES	A5	529935	01-08-85
			ES	A1	8505673	01-10-85
			ES	A1	529933	16-10-85
			ES	A1	8506020	16-10-85
			ES	A1	8506021	16-10-85
			ES	A1	8506309	01-11-85
			ES	A5	529933	15-11-85
			ES	A1	8600934	16-02-86
			FI	A0	833151	05-09-83
			FI	A	833151	10-03-84
			FI	B	83513	15-04-91
			FI	C	83513	25-07-91
			GR	A	79059	02-10-84
			HU	B	196986	28-02-89
			IE	B	55898	14-02-91
			IL	A0	69601	30-11-83
			IL	A0	80848	31-03-87
			IL	A0	80849	31-03-87
			IL	A1	69601	31-08-87
			IL	A1	80848	30-09-88
			IL	A1	80849	31-10-88
			JP	A2	59067269	16-04-84
			JP	A2	1146880	08-06-89
			JP	A2	4210961	03-08-92
			JP	B4	6062561	17-08-94
			JP	A2	7070111	14-03-95
			JP	B4	7042284	10-05-95
			JP	B4	7080770	30-08-95
			JP	A2	8311061	26-11-96
			JP	B2	3704984	26-01-99
			KR	B1	8901424	03-05-89
			NO	A	833206	12-03-84
			NO	B	164416	25-06-90
			NO	C	164418	03-10-90
			NZ	A	205529	06-05-86
			NZ	A	213054	09-05-86
			PH	A	21530	16-11-87
			PT	A	77308	01-10-83
			PT	B	77308	09-04-86
			ZA	A	8306357	25-04-84
			US	A	4665079	12-05-87
			US	A	4777175	11-10-88
			US	A	5281612	25-01-94
			CS	B2	246083	16-10-86
			CS	B2	246084	16-10-86
			CS	B2	247180	18-12-86
			SU	A3	1314954	30-05-87
			SU	A3	1321376	30-06-87
			SU	A3	1360584	15-12-87
			US	A	4771054	13-09-88
			AT	E	46997	15-01-90
			AU	A1	38619/85	22-08-85
			AU	B2	568004	10-12-87

Form PCT/ISA/210 (patent family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00185

			CA	A1	1289956	01-10-91
			DE	C0	3574972	01-02-90
			DK	A0	687/85	14-02-85
			DK	A	687/85	16-08-85
			DK	B	161889	26-08-91
			DK	C	161889	03-02-92
			EP	A0	153163	28-08-85
			EP	A3	153163	29-01-86
			EP	B1	153163	27-12-89
			ES	A1	540441	01-05-87
			ES	A5	540441	01-06-87
			ES	A1	8705422	16-07-87
			FI	A0	850631	15-02-85
			FI	A	850631	16-08-85
			FI	B	83312	15-03-91
			FI	C	83312	25-06-91
			GR	A	850396	14-06-85
			HU	A2	37149	28-11-85
			IE	B	58098	30-06-93
			IL	A0	74286	31-05-88
			IL	A1	74286	31-07-88
			JP	A2	60214773	28-10-85
			JP	B4	7055945	14-06-95
			JP	A2	7173160	11-07-95
			JP	B2	2604124	30-04-97
			KR	B1	90004995	16-07-90
			NO	A	850614	19-08-85
			NO	B	161370	02-05-89
			NO	C	161370	09-08-89
			NZ	A	211137	30-08-88
			PH	A	20942	05-06-87
			PT	A	79971	01-03-85
			PT	B	79971	02-02-87
			ZA	A	8500854	24-09-86
EP A2	153165	28-08-85	AU	A1	38563/85	22-08-85
			AU	B2	581204	16-02-89
			CA	A1	1220824	21-04-87
			DE	C0	3580855	24-01-91
			EP	A3	153165	03-09-86
			EP	B1	153165	12-12-90
			JP	A2	61010333	17-01-86
			US	A	4573170	25-02-86
			ZA	A	8500743	25-09-85
EP A2	529688	03-03-93	AT	E	96791	15-11-93
			AT	E	160141	15-11-97
			AU	A1	41006/89	08-03-90
			AU	B2	619891	06-02-92
			CA	A1	1336090	27-06-95
			CN	A	1040790	28-03-90
			CN	A	1100095	15-03-95
			CN	B	1028102	05-04-95
			CN	B	1036193	22-10-97
			DE	C0	68910441	09-12-93
			DE	T2	68910441	03-03-94
			DE	C0	68928447	18-12-97
			DE	T2	68928447	18-06-98
			DK	A0	4262/89	30-08-89
			DK	A	4262/89	01-03-90
			EP	A1	357047	07-03-90
			EP	A3	529688	10-03-93
			EP	B1	357047	03-11-93
			EP	B1	529688	12-11-97
			ES	T3	2061845	16-12-94
			ES	T3	2111029	01-03-98
			FI	A0	894045	29-08-89
			FI	A	894045	01-03-90
			FI	A	934016	14-09-93
			FI	A0	934016	14-09-93
			FI	B	92703	15-09-94
			FI	C	92703	27-12-94
			IE	B	63492	03-05-95
			IL	A0	91474	29-04-90
			IL	A1	91474	30-05-94
			IN	A	170262	07-03-92
			JP	A2	8333337	17-12-96
			NO	A0	893453	29-08-89
			NO	A	893453	01-03-90
			NO	B	177638	17-07-95
			NO	C	177638	25-10-95
			NZ	A	230484	25-06-91
			PT	A	91602	08-03-90
			PT	B	91602	31-05-95
			US	A	5286723	15-02-94
			US	A	5508426	16-04-96
			JP	A2	3095176	19-04-91

Form PCT/ISA/210 (patent family annex) (July 1998)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00185

HR	A1	930082	30-04-96
SI	A	8911674	31-10-97
YU	A	1674/89	30-04-91
RU	C1	2094432	27-10-97
ZA	A	8906607	27-03-91